IV. REMARKS

Claim Status

Claims 1-40 are in the application. Claims 1-2, 4, 6-8, 27-29 and 31 are currently amended. Claims 3, 5, 9-26, 30 and 32-40 are cancelled.

Claim Rejections - 35 USC § 112

Claims 11 and 32 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

These claims have been cancelled.

Claim Rejections - 35 USC § 102

Claims 1-8,10,11,17,18,21,23-30,32,36 and 40 stand rejected under 35 U.S.C. 102(b) as being anticipated by *Alaux et al.* (WO/2000/033835) as stated in the office action mailed on 7/25/06.

Applicant traverses this ground for rejection.

The Examiner adopts the position in each of the following 35 USC 102 rejections, that the prior art discloses identical compositions and therefore the properties of the claimed compositions will also be anticipated by the prior art teaching, since the properties, namely the breaking strength of 500N, are inseparable from its composition. Therefore, the Examiner argues, if the prior art teaches the composition, then the properties are also taught by the prior art and the burden is therefore shifted to Applicant to show that the prior art product does not possess the same properties as the instantly claimed product.

Applicant has accepted and surmounted this burden by the information presented herein and by providing the Declaration of the inventor demonstrating that the claimed

properties are dependent upon not only the composition but on the method of manufacturing the composition. Applicant has demonstrated that the properties can only be obtained by thermoforming under specified conditions of time and temperature.

The dosage forms according to the invention are distinguished from the dosage forms of the prior art in that the cited references do not describe a thermoformed dosage form wherein the active ingredient with abuse potential is present in a controlled release matrix of a polymer comprising polyalkylene oxide having a molecular weight of at least 0.5 million.

Claim 1 has been limited to where

1] the product is thermoformed

2] the active ingredient (A) is selected from the group consisting of opiates and opioids (original claim 10; specification, page 4, lines 23-27);

3] the synthetic or natural polymer (C) comprises a polyalkylene oxide having a molecular weight of at least 0.5 million according to rheological measurements (original claims 4 and 5; specification, page 11, lines 7-10); and

4] the active ingredient (A) is present in a controlled release matrix of component (C) (original claims 24 to 26; specification, page 35, line 28 to page 36, line 3 and page 36, lines 27-31).

Alaux et al. is silent regarding the applicability of polyalkylene oxide, let alone polyalkylene oxide having a molecular weight of at least 0.5 million.

As *Alaux et al.* does not disclose each element of the claimed composition, *Alaux et al.* does not anticipate the claimed composition.

Claims 1-6,10-11, 17-18, 21, 23-27,30-32 and 40 stand rejected under 35 U.S.C. 102(b) as being anticipated by Kuczynski et al. (US 5,866,164) as stated in the office action mailed on 7/25/06.

Applicant traverses this ground for rejection.

Kuszynski at al. discloses osmotic dosage forms that contain polyalkylene oxide having a molecular weight of at least 0.5 million. According to *Kuszynski et al. the* composition of the drug layer ("first composition") and the composition of the push layer ("second composition") are pressed in a standard tablet press into a bilayered core, with the first composition and the second composition in bilayered arrangement *(Kuszynski et al.,* column 2, line 66 to column 3, line 3 column 3, line 66 to column 4, line 7). However, the osmotic dosage forms according to *Kuszynski et al.* are not thermoformed.

In contrast to applicant's compositions per amended claim 1, the release profile of the osmotic dosage forms according to *Kuszynski et al.* does not rely on a controlled-release matrix, but on the expansion of the water-swellable high molecular polyalkylene oxides in the push layer, which does not contain the drug.

In other words, in the dosage forms according to the subject invention the high molecular weight polyalkylene oxide serves as a controlled-release matrix thereby retarding the release profile of the drug. In contrast thereto, in the osmotic dosage forms according to *Kuszynski at al. a* semi-permeable membrane hinders the drug from being released and the swelling of the high molecular weight polyalkylene oxide rather causes the drug to leave the dosage form by pushing it through an orifice in the semi-permeable membrane.

Therefore, the effect of the high molecular weight polyalkylene oxide in the matrix dosage forms of the subject invention and in the osmotic dosage forms of the prior art is just oppositional.

As *Kuszynski et al.* does not disclose each element of the claimed composition, *Kuszynski et al.* does not anticipate the claimed composition.

Claims 1-8,10-18 and 21-34,36,39 and 40 stand rejected under 35 U.S.C. 102(e) as being anticipated by *Oshlack et al.* (US 2003/0064099A1).

Applicant traverses this ground for rejection.

Oshlack et al. mentions polyalkylene oxide having a molecular weight of at least 0.5 million. Nevertheless, the only disclosure of these polymers is exclusively concerned with osmotic dosage forms *(Oshlack et al.,* [0148]-[0159]), which, however, are not thermoformed.

In another context, *Oshlack et al.* mentions methods for the preparation of matrix formulations which methods may be regarded as thermoforming, such as melt-extrusion *(Oshlack et* al., [0111]). These matrix materials according to *Oshlack at al.,* however, do not encompass polyalkylene oxides *(Oshlack et al.,* [0097]).

Furthermore, in the dosage form according to amended claim 1 of the present application, the active ingredient (A) is present in a controlled-release matrix of component (C). The active ingredient is embedded in the high molecular weight polyalkylene oxide that in turn serves as a retardant agent (specification, page 35, lines 13-19).

In contrast thereto, the release profile of the osmotic dosage forms according to *Oshlack at al.* does not rely on a controlled-release matrix, but on the expansion of the water-swellable high molecular polyalkylene oxides in the push layer, which does not contain the drug.

In other words, in the dosage forms according to the subject invention the high molecular weight polyalkylene oxide serves as a controlled-release matrix thereby retarding the release profile of the drug. In contrast thereto, in the osmotic dosage forms

according to and *Oshlack et al. a* semi-permeable membrane hinders the drug from being released and the swelling of the high molecular weight polyalkylene oxide rather causes the drug to leave the dosage form by pushing it through an orifice in the semi-permeable membrane.

Therefore, the effect of the high molecular weight polyalkylene oxide in the matrix dosage forms of the subject invention and in the osmotic dosage forms of the prior art is just oppositional.

As *Oshlack et al.* does not disclose each element of the claimed composition, *Oshlack et al.* does not anticipate the claimed composition.

Claim Rejections - 35 USC § 103

Claims 1-8 and 10-40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Alaux et al.* (WO/2000/033835) in view of the combined disclosures of *Oshlack et al.* (US 2003/0064099A1), and *Porter* (US 4,175,119) as stated in the office action mailed on 7/25/06.

Applicant's assertions regarding *Alaux et al.* and *Oshlack et al.* are disclosed above.

The Porter (US 4,175,119) reference is used to show that the emetic, such as emetine (major alkaloid of ipecac syrup) could be a useful agent for the deterrence of abusing/incorrectly consuming a composition that has abuse potential.

However, since the claims are limited to polyalkylene oxides and as neither *Alaux et al.* nor *Oshlack et al.* disclose these compounds having the required breaking strength, *Porter* does not cure this defect.

Claims 1-8, 10-18, 21-36, 39 and 40 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Alaux et al.* (WO/2000/033835) in view of *Oshlack et al.* (US 2003/0064099A1) and *Sackler* (US 2004/0170567).

Applicant's assertions regarding *Alaux et al.* and *Oshlack et al. are* disclosed above.

The *Sackler* reference is used to show that an abuse proof dosage form containing a medicament, such as an opiate, an inactivating agent, such as a dye, etc., irritating agents, such as mustard oil is known The sustained release tablets may contain a carrier, such as carboxymethyl cellulose, waxes, etc.

However, since the claims are limited to polyalkylene oxides and as neither *Alaux et al.* nor *Oshlack et al.* disclose these compounds having the required breaking strength, *Sackler* does not cure this defect.

Double Patenting

Claims 1-8 and 10-40 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 and 36 of copending Application No. 10/567,594. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-8 and 10-40 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30 of copending Application No. 11/349,537. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-8,10,27-31 and 36 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1- 5,7-9,17 and 18 of copending Application No. 10/890,704. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-3,10-20,22-27,30,32-38 and 40 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16,18-26,31,36,37 and 38 of copending Application No. 11/113,118. This

is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant notes that the claims of co-pending U.S. patent application serial no. 11/113,118 (US 2005/0214223) do not contain the feature that the dosage forms have a breaking strength of 500 N.

Claims 1-7,10,11,30,31 and 36 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5,7,9-11,19 and 20 of copending Application No. 10/890,703 in view of W02004/026262. This is a provisional obviousness-type double patenting rejection.

Claims 1-8,11,17,20-32,36 and 38-40 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 10/890,707 in view of W02004/026262. This is a provisional obviousness-type double patenting rejection.

Applicant notes that as no claims have been allowed, these grounds for rejection need now be responded to until such time as allowable subject matter is indicated.

Osmotic dosage forms

Osmotic dosage forms use the principle of osmosis to deliver drugs from the tablet dosage form in a controlled manner, typically in a zero-order profile.

The general structure of an osmotic dosage form of the type as described in *Kuszynski et al.* and *Oshlack et al.* can be found at

http://www.drugdeliveryreport.com/articles/ddcr_w2004_article3.pdf

The system comprises a bilayer tablet core consisting of one push layer and one drug layer. The drug layer contains the drug and osmotic agents. The push layer contains water-swellable polymers, osmotic agents and, additionally, an opioidantagonist

(Kuczynski at al.) and an aversive agent *(Oshlack at al),* respectively. A semi-permeable membrane surrounds the tablet core and at least one orifice is drilled in it on the drug layer side.

Upon ingestion of the system, water is drawn into the drug layer. The push layer expands when water is drawn in due to the presence of water-swellable polymers. The expanding push-layer delivers the drug through the exit orifice at a controlled rate into the gastrointestinal tract.

Summing up, in osmotic dosage forms controlled release is not achieved by matrix retardation, but by swelling of the push layer thereby pushing the drug out of the dosage form.

The release profile of the osmotic dosage forms according to *Kuszynski et al.* and *Oshlack at al.* does not rely on a controlled-release matrix, but on the expansion of the water-swellable high molecular polyalkylene oxides in the push layer, which does not contain the drug.

In other words, in the dosage forms according to the subject invention the high molecular weight polyalkylene oxide serves as a controlled-release matrix thereby retarding the release profile of the drug. In contrast thereto, in the osmotic dosage forms according to *Kuszynski et al.* and *Oshlack et al. a* semi-permeable membrane hinders the drug from being released and the swelling of the high molecular weight polyalkylene oxide rather causes the drug to leave the dosage form by pushing it through an orifice in the semi-permeable membrane.

In conclusion, the cited references do not disclose or suggest a thermoformed dosage form that contains polyalkylene oxide having a molecular weight of at least 0.5 million, wherein the active ingredient is present in a controlled release matrix.

Breaking Strength

The Examiner may not be aware of the breaking strength of conventional oral dosage forms and may not recognize that oral dosage forms having a breaking strength of at least 500 N are very special.

As set forth in applicants last response, the mechanical properties of the dosage form according to the invention, particularly the breaking strength of at least 500 N, may not automatically be achieved by simply processing components (A), (C), optionally (B) and optionally (D) by means of conventional methods for the preparation of pharmaceutical dosage forms.

The importance of this point is highlighted by the fact that the various apparatus used for preparation of the dosage forms must be selected and critical processing parameters must be adjusted, particularly pressure/force, temperature and time.

The inventive dosage forms exhibiting the desired properties may be obtained only if, during preparation of the dosage form, the components are exposed to a sufficient pressure at a sufficient temperature for a sufficient period of time. Thus, regardless of the apparatus used, the process protocols must be adapted in order to meet the required criteria.

Therefore, the breaking strength is separable from the composition and depends as well on the method of manufacturing the composition.

When identical mixtures containing an active ingredient with abuse potential (A) and a sufficient quantity of a synthetic or natural polymer (C) are processed

1] in accordance with a conventional method for the manufacture of pellets, such as direct compression at ambient temperature, or

2] the examples of the present application, e.g. in a tabletting tool at a temperature of 80-90°C by maintaining pressure for at least 15 seconds,

only in the latter case a breaking strength of at least 500 N will be achieved.

There are various items of information in the prior art indicating that conventional dosage forms do not inherently realize a breaking strength of at least 500 N.

Conventional tablets typically have a breaking strength well below 200 N. The breaking strength of conventional round tablets may be estimated according to the following empirical formula:

Breaking Strength [in N] = *10 x Diameter Of The Tablet* [in mm].

Thus, according to this empirical formula, a round tablet having a breaking strength of at least 500 N would require a diameter of at least 50 mm (about 2 inches). Such a tablet, however, could not be swallowed.

Of course, the above empirical formula does not apply to the dosage forms of the present invention, which are not conventional.

In this regard it is also interesting to note that the actual mean chewing force is about 220 N (e.g., P.A. Proeschel et al., J Dent Res, 2002, 81(7), 464468, copy attached). This means that conventional tablets having a breaking strength well below 200 N may be crushed upon chewing, whereas the dosage forms according to the invention may not.

Another fact indicating that a breaking strength of 500 N is something very unusual is concerned with the upper limit of the measurable ranges of the breaking strength that may be measured by means of conventional breaking strength testers, confusingly also referred to as "tablet hardness testers", although the hardness of a tablet has nothing to do with its breaking strength.

Modern testers are usually calibrated in kiloponds or newtons. The relationship between these units of force is 1 kilopond (kp) = 1 kilogram-force (kgf) = 9.81 N.

In the following table we have summarized some technical data available from the internet concerning conventional testers currently available on the market (excerpts from the internet pages are attached):

	Product Name/ Manufacturer)	Measurable Range		Internet address
		Unit published	In Newton	
1	VK 200 (Varian Inc.)	0.4 to 35 kp	3.9 to 343	*http:/www.varianinc.com/image/vimegeldocs/products/dissolution/shared/specs/VK 200.pdf*
2	THT10 (G.B. Caleva Ltd.)	3-500 N	3 to 500	*http://www.gb-calevaco.uk/net-controlIviewPage.as•?intNodeId=78*
3	QM-HTD (CI Electronics Ltd.)	2.0 to 30 kp	19 to 294	*http://www.accompacting.com/html/ci/hardness_ Tester QMHTD.html*
4	PTB 302 (Pharma Test Apparatebau GmbH)	300 N, can be upgraded to 500 N	300, can be upgraded to 500	*http://www.pharma-test/en/products/p80_4.htm*
5	DIGI-TAB (Blue Steel Engineers PVT Ltd.)	0.3 to 50 kg	2.9 to 490	http://www.bluesteeltester.com/PDF/DIGI-TAB.pdf
6	C-DHT 200 (Campbell Electronic)	0.5 to 50 kg	4.9 to 490	http://www.campbellelectronics.com/tablethardnesstester/200.html
7	MHT-100 (LabECX Inc.)	Up to 5000 N	Up to 500	http://www.labecx.com/t-PortableTabletHardnessTester.aspx?gclid=CJWw0ez1gosCFQJOZwodt2-1aA
8	HT-300	05. to 30 kp	4.9 to 294 7.8	*http://www.pharmaceuticalonl*

	(Key Inyternati onal Inc.)	0.8 to 50 kp	to 490	*ne.com*/Content/ProductShowc ase/product.asp?DocID=%7B9 F62E54E-FFE04C94-995C-BD1412FD9AA4%7D

It becomes evident from the above measurable ranges that dosage forms exhibiting a breaking strength of at least 500 N may not be investigated by means of these conventional testers, as they are out of range, i.e. beyond the upper limit that may be measured by means of these testers.

Applicants have performed experimental tests to demonstrate that the conventional methods for the preparation of dosage forms, such as disclosed in *Kuszynski et al,*. do not yield dosage forms having a breaking strength of at least 500 N.

Enclosed is a Declaration by Dr. Johannes Bartholomus, co-inventor and head of applicants pharmaceutical development division.

The Declaration confirms that conventional dosage forms exhibit breaking strengths well below 500 N.

Furthermore, the Declaration provides experimental evidence that the processing of pharmaceutical compositions which contain significant amounts of polyalkylene oxide having a molecular weight of at least 0.5 million according to conventional processes and process protocols does not yield dosage forms having a breaking strength of at least 500 N.

This is in accordance with the findings of *Maggi et al.,* cited in co-pending U.S. 11/462,216.

For all of the foregoing reasons, it is respectfully submitted that all of the claims now present in the application are clearly novel and patentable over the prior art of record, and are in proper form for allowance. Accordingly, favorable reconsideration and

allowance is respectfully requested. Should any unresolved issues remain, the Examiner is invited to call Applicants' attorney at the telephone number indicated below.

The Commissioner is hereby authorized to charge payment of a two-month extension of time and any fees associated with this communication or credit any over payment to Deposit Account No. 16-1350.

Respectfully submitted,

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